



08/31/00

TELEPHONE: (703) 243-6333
 CABLE: USALAW
 INT'L TELEX: 64191
 TELECOPIER: (703) 243-6410

LAW OFFICES
 MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
 ARLINGTON COURTHOUSE PLAZA I
 SUITE 1400
 2200 CLARENDON BOULEVARD
 ARLINGTON, VIRGINIA 22201

U.S. PTO
 09/654227
 08/31/00

Atty's Docket No. PLOVIN-1-A

Applicant(s) : Wolfgang HEIL et al.
 For : PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE

The Honorable Commissioner
 of Patents and Trademarks
 Washington, D.C. 20231

SUBMISSION OF APPLICATION UNDER 37 C.F.R. §1.53(f)

Sir:

Herewith is the above-identified application for Letters Patent including:

Applicant(s) Name(s) : Wolfgang HEIL; Berlin, Germany
 Juergen HILMAN; Berlin, Germany
 Ralph LIPP; Berlin, Germany
 Renate HEITHECKER; Berlin, Germany

Assignee (by unrecorded assignment) : Schering Aktiengesellschaft

Pages of Application: Specification - 15
 Claims - 5
 Abstract - 1
 Sheets of Drawings - 5

NO DECLARATION IS ATTACHED.

☐ Preliminary Amendment☒ The benefit under 35 U.S.C. §119 is claimed of the filing date of:

U.S. Provisional Application filed August 31, 2000

☐ A certified copy of the priority document(s) is attached.

Respectfully submitted,

By: 

Anthony J. Zelano, Reg. No. 27,969
 Representative Capacity

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
 Arlington Courthouse Plaza I
 2200 Clarendon Boulevard, Suite 1400
 Arlington, Virginia 22201
 (703) 812-5311 [direct dial]
 Internet Address: zelano@mwzb.com

Filed: August 31, 2000

09/654227 08/31/00

1. **Introduction**
 2. **Method**
 3. **Results**
 4. **Discussion**
 5. **Conclusion**
 6. **References**
 7. **Appendix**
 8. **Table 1**
 9. **Table 2**
 10. **Table 3**
 11. **Table 4**
 12. **Table 5**
 13. **Table 6**
 14. **Table 7**
 15. **Table 8**
 16. **Table 9**
 17. **Table 10**
 18. **Table 11**
 19. **Table 12**
 20. **Table 13**
 21. **Table 14**
 22. **Table 15**
 23. **Table 16**
 24. **Table 17**
 25. **Table 18**
 26. **Table 19**
 27. **Table 20**
 28. **Table 21**
 29. **Table 22**
 30. **Table 23**
 31. **Table 24**
 32. **Table 25**
 33. **Table 26**
 34. **Table 27**
 35. **Table 28**
 36. **Table 29**
 37. **Table 30**
 38. **Table 31**
 39. **Table 32**
 40. **Table 33**
 41. **Table 34**
 42. **Table 35**
 43. **Table 36**
 44. **Table 37**
 45. **Table 38**
 46. **Table 39**
 47. **Table 40**
 48. **Table 41**
 49. **Table 42**
 50. **Table 43**
 51. **Table 44**
 52. **Table 45**
 53. **Table 46**
 54. **Table 47**
 55. **Table 48**
 56. **Table 49**
 57. **Table 50**
 58. **Table 51**
 59. **Table 52**
 60. **Table 53**
 61. **Table 54**
 62. **Table 55**
 63. **Table 56**
 64. **Table 57**
 65. **Table 58**
 66. **Table 59**
 67. **Table 60**
 68. **Table 61**
 69. **Table 62**
 70. **Table 63**
 71. **Table 64**
 72. **Table 65**
 73. **Table 66**
 74. **Table 67**
 75. **Table 68**
 76. **Table 69**
 77. **Table 70**
 78. **Table 71**
 79. **Table 72**
 80. **Table 73**
 81. **Table 74**
 82. **Table 75**
 83. **Table 76**
 84. **Table 77**
 85. **Table 78**
 86. **Table 79**
 87. **Table 80**
 88. **Table 81**
 89. **Table 82**
 90. **Table 83**
 91. **Table 84**
 92. **Table 85**
 93. **Table 86**
 94. **Table 87**
 95. **Table 88**
 96. **Table 89**
 97. **Table 90**
 98. **Table 91**
 99. **Table 92**
 100. **Table 93**
 101. **Table 94**
 102. **Table 95**
 103. **Table 96**
 104. **Table 97**
 105. **Table 98**
 106. **Table 99**
 107. **Table 100**
 108. **Table 101**
 109. **Table 102**
 110. **Table 103**
 111. **Table 104**
 112. **Table 105**
 113. **Table 106**
 114. **Table 107**
 115. **Table 108**
 116. **Table 109**
 117. **Table 110**
 118. **Table 111**
 119. **Table 112**
 120. **Table 113**
 121. **Table 114**
 122. **Table 115**
 123. **Table 116**
 124. **Table 117**
 125. **Table 118**
 126. **Table 119**
 127. **Table 120**
 128. **Table 121**
 129. **Table 122**
 130. **Table 123**
 131. **Table 124**
 132. **Table 125**
 133. **Table 126**
 134. **Table 127**
 135. **Table 128**
 136. **Table 129**
 137. **Table 130**
 138. **Table 131**
 139. **Table 132**
 140. **Table 133**
 141. **Table 134**
 142. **Table 135**
 143. **Table 136**
 144. **Table 137**
 145. **Table 138**
 146. **Table 139**
 147. **Table 140**
 148. **Table 141**
 149. **Table 142**
 150. **Table 143**
 151. **Table 144**
 152. **Table 145**
 153. **Table 146**
 154. **Table 147**
 155. **Table 148**
 156. **Table 149**
 157. **Table 150**
 158. **Table 151**
 159. **Table 152**
 160. **Table 153**
 161. **Table 154**
 162. **Table 155**
 163. **Table 156**
 164. **Table 157**
 165. **Table 158**
 166. **Table 159**
 167. **Table 160**
 168. **Table 161**
 169. **Table 162**
 170. **Table 163**
 171. **Table 164**
 172. **Table 165**
 173. **Table 166**
 174. **Table 167**
 175. **Table 168**
 176. **Table 169**
 177. **Table 170**
 178. **Table 171**
 179. **Table 172**
 180. **Table 173**
 181. **Table 174**
 182. **Table 175**
 183. **Table 176**
 184. **Table 177**
 185. **Table 178**
 186. **Table 179**
 187. **Table 180**
 188. **Table 181**
 189. **Table 182**
 190. **Table 183**
 191. **Table 184**
 192. **Table 185**
 193. **Table 186**
 194. **Table 187**
 195. **Table 188**
 196. **Table 189**
 197. **Table 190**
 198. **Table 191**
 199. **Table 192**
 200. **Table 193**
 201. **Table 194**
 202. **Table 195**
 203. **Table 196**
 204. **Table 197**
 205. **Table 198**
 206. **Table 199**
 207. **Table 200**
 208. **Table 201**
 209. **Table 202**
 210. **Table 203**
 211. **Table 204**
 212. **Table 205**
 213. **Table 206**
 214. **Table 207**
 215. **Table 208**
 216. **Table 209**
 217. **Table 210**

Filed: August 31, 2000

PRELIMINARY AMENDMENT

Sir:

Prior to examination of the above-identified application, please amend the application as follows:

Page 1, line 1, please insert the following:

--This application claims the benefit of the filing date of the provisional application filed August 31, 1999, corresponding to converted non-provisional application Serial Number 09/386,274.--

Claim 3, line 1: Delete “or 2”.

Claim 12, line 1: Delete “or 11”.

Claim 20, line 1: Delete “or 19”.

The purpose of this Preliminary Amendment is to eliminate multiply dependent of the claims and the fees associated therewith.

Respectfully submitted,

Anthony J. Zelano, Registration No. 27,969
Attorney for Applicants
MILLEN, WHITE, ZELANO & BRANIGAN, P. C.
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703)812-5311
Internet address: zelano@mwzb.com

Filed: August 31, 2000

AJZ/tal:K:\PAT\Plovin\1 A\preliminary amendment.wpd

PLOVIN-1-A

A PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE

FIELD OF THE INVENTION

- 5 The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

10 BACKGROUND OF THE INVENTION

Oral contraceptives containing a combination of a gestagen and an estrogen component have been used since the 1960's. The earliest contraceptive preparations consisted of 21 tablets containing the combination of active agents and 7 tablets containing no active
15 agent, and the amount of each active agent was the same in each tablet (the so-called one-phase preparations). Subsequently, preparations were developed that consisted of tablets containing different amounts and ratios of the active agents over the cycle of administration (the so-called multiple-phase preparations).

- 20 Contraceptive reliability is mainly provided by the gestagen component. The daily dosage should be at least the minimum of what is needed for the gestagen in question to inhibit ovulation effectively. The estrogen component acts to increase the ovulation inhibitory effect of gestagen and to ensure cycle stability. Since the introduction of oral contraceptives, the daily dosage of gestagen has been reduced through the development
25 of new and more efficient gestagens than were present in the earlier contraceptive preparations. It has also been possible to reduce the daily dosage of estrogen.

6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) is known from DE 26 52 761 in which its use as a diuretic compound is disclosed.

30

- In DE 30 22 337, the gestagen-like activity of the compound and its consequent utility as a contraceptive agent is described at dosage levels of 0.5-50 mg of drospirenone per day. It is also noted that the mechanism of action of the compound is very similar to that of the natural corpus luteum hormone progesterone, and that it does not give rise to increased
35 blood pressure for which reason it may be administered to women who have or are at risk

of developing increased blood pressure. It is further described that drospirenone may be administered together with ethinylestradiol in an amount of 0.03-0.05 mg per day.

DE 30 51 166 discloses the use of the drospirenone for the treatment of gynaecological
5 irregularities and for contraception at a dosage level of 0.5-50 mg per day.

EP 398 460 discloses the use of drospirenone for the treatment of androgen-induced disorders, aldosterone-induced disorders and hormonal irregularities as well as for contraception at dosage levels of 0.5-50 mg, preferably 1-10 mg per day. Ethinylestradiol
10 may be co-administered at a level of 0.02-0.04 mg per day.

US 5,756,490 discloses pharmaceutical combination preparations comprising 23 or 24 dosage units containing a combination of a gestagen and an estrogen and 4-10 dosage units containing estrogen alone. Drospirenone is mentioned as a possible, but not
15 preferred, gestagenic compound and ethinylestradiol is mentioned as a possible, but not preferred, estrogenic compound.

SUMMARY OF THE INVENTION

- 20 In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.
- 25 Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, $6\beta,7\beta;15\beta,16\beta$ -dimethylene-3-oxo- 17α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17α -ethinylestradiol (ethinylestradiol) in an amount corresponding to
30 a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane

carbolactone as disclosed in WO 98/24801. Likewise, it is envisaged that esters or ethers of ethinylestradiol may be included in the composition.

In a further aspect, the invention relates to a method of inhibiting ovulation in a mammal,
 5 in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said mammal.

10 In a still further aspect, the invention relates to the use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily
 15 dosage, on administration of the composition, of from about 0.01 to about 0.05 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described with reference to the drawings in which
 20

Fig. 1 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, V1-V7 being batches containing micronized drospirenone, and V8 being a batch containing macrocrystalline drospirenone;

25 Fig. 2 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, different lines representing different test batches;

Fig. 3 is a graph showing the in vitro dissolution rate of drospirenone from film-coated tablets, different lines representing different test batches;
 30

Fig. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and

Fig. 5 is a graph showing the in vitro dissolution rate of ethinylestradiol from film-coated
 35 tablets, different lines representing different test batches.

007E80 2245950

DETAILED DISCLOSURE OF THE INVENTION

Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or
5 WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various
pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid
conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the
compound, it is therefore advantageously provided in a form that promotes rapid
dissolution thereof.

10

It has surprisingly been found that when drospirenone is provided in micronized form (so
that particles of the active substance have a surface area of more than 10,000 cm²/g, and
the following particle size distribution as determined under the microscope: not more than
2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20

15 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid
dissolution of the active compound from the composition occurs in vitro ("rapid
dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in
particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation
containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII
20 Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing
the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g.
methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed
by incorporation of the particles containing drospirenone on their surface in the
composition.

25

Without wishing to be limited to any particular theory, it appears that the in vitro
dissolution rate of drospirenone is connected to the dissolution rate in vivo resulting in
rapid absorption of drospirenone in vivo on oral administration of the compound. This is
an advantage because isomerization of the compound in the gastric environment and/or
30 hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the
compound.

With respect to ethinylestradiol which is also a sparingly soluble substance, though less
sensitive to degradation than drospirenone under conditions prevailing in the
35 gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed

from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of $\leq 15.0 \mu\text{m}$, 99% of the particles have a diameter of $\leq 12.5 \mu\text{m}$, 95% of the particles have a diameter of $\leq 10.0 \mu\text{m}$, and 50% of the particles have a diameter of $\leq 3.0 \mu\text{m}$. Furthermore, no particle is larger than $20 \mu\text{m}$, and ≤ 10 particles have a diameter of $\geq 15 \mu\text{m}$ and $\leq 20 \mu\text{m}$.

To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above.

Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

In a particular embodiment, the invention relates to a pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage

units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

5

In one embodiment, the preparation further comprises 7 or less said daily dosage units containing no active agent. Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested. For compliance reasons, however, it may be preferred to include an appropriate number of blanks in the preparation, in which case the total number of daily dosage units in the preparation is at least 28. The inclusion of blanks, or the pill-free days, will then trigger withdrawal bleeding.

The preparation may be a one-phase composition, i.e. a preparation wherein the amounts of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing no active agent may then be 7, 6, 5 or 4, as the case may be. In a further embodiment of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

In an alternative embodiment, the invention relates to a contraceptive preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of

007220 22245960

By including an appropriate number of dosage units comprising ethinylestradiol alone, a

10

15

20

25

30

2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4 consecutive days.

Alternatively, the present method comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

In this alternative method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. In a further embodiment of the method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

For use according to the invention, the pharmaceutical preparation may suitably be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

As indicated above, the preparation may further comprise 7 or less daily dosage units containing no active agent (or may contain 7 or less empty "places", e.g. in the form of empty blisters in a blister pack, marking the days on which no daily dosage units are administered).

Alternatively, the pharmaceutical preparation may be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days,

- 5 wherein at least 21 of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

10

The composition of the invention may be formulated in any manner known in the pharmaceutical art. In particular, as indicated above, the composition may be formulated by a method comprising providing drospirenone and, if desired, ethinylestradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an

- 15 inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration. Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as wheat, corn or
20 potato starch, modified starch or sodium starch glycolate, lubricants such as talc, magnesium stearate, calcium stearate, colloidal silica or stearic acid, and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose or gelatin, for making oral dosage forms such as tablets, pills or capsules.

25

- Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, filler such as sucrose, sorbitol, xylitol,
30 glucose or lactose, a colorant such as titanium hydroxide, etc.

The present composition may also be formulated in liquid form, e.g. as a solution, suspension or emulsion, together with conventional diluents or excipients in a manner known per se in the pharmaceutical art.

35

A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for

5 particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain

10 no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making

15 implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers, ethylene vinylacetate, polyethylene or polypropylene.

Where transdermal formulations are concerned, they may be prepared in the form of

20 matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper

25 coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or

30 more substances that enhance absorption through the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous

Absorption", Marcel Dekker Inc., New York - Basel, 1983, or YW Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York - Basel, 1987.

The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXPERIMENTAL

Example 1

10

Preparation of tablets containing drospirenone and ethinylestradiol

Tablet cores of the following composition

15	micronized drospirenone	3.00 mg
	micronized ethinylestradiol	0.03 mg
	lactose monohydrate	48.17 mg
	corn starch	14.40 mg
	modified starch	9.60 mg
20	polyvinylpyrrolidone 25,000	4.00 mg
	magnesium stearate	0.80 mg

were prepared by charging a fluidized bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 micronized drospirenone, 0.066 kg micronized ethinylestradiol and 105.974 kg lactose monohydrate and activating the fluidized bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water was sprayed continuously onto the fluidized bed while drying by heating the air stream of the fluidized bed. At the end of the process 1.76 kg magnesium stearate was sucked into the granulator and mixed with the granules by maintaining the fluidized bed. The resulting granulate was pressed into tablet cores by compression using a rotary tablet press.

2.22464 kg of hydroxypropylmethylcellulose and 0.44528 macrogol 6000 were dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.22430 kg titanium dioxide and 0.06050 kg ferric oxide pigment were suspended in 10.26 kg purified water with stirring and

homogenized. The solution and suspension were combined and used to coat the tablet cores by continuous application of the coating suspension in a coater.

Example 2

5

Dissolution of drospirenone from tablets

The rate of dissolution of drospirenone from the tablets prepared in Example 1 was determined by the USP XXIII Paddle Method using a USP Dissolution Test Apparatus 2
10 including 6 covered glass vessels and 6 paddles. Tablets were placed in 900 ml water at a temperature of 37°C ($\pm 0.5^\circ\text{C}$) and stirred at 50 rpm.

The results appear from Figs. 1, 2 and 4. From Fig. 1, it appears that the batch numbered V8 containing macrocrystalline drospirenone (but otherwise identical to the tablets prepared in Example 1) exhibited an extremely slow dissolution rate of drospirenone,
15 whereas all batches containing micronized drospirenone exhibited a dissolution rate of more than 70% within 30 minutes.

Fig. 2 and Fig. 4 shows the results of dissolution of drospirenone from tablet cores and film-coated tablets, respectively. In both cases more than 70% of the active agent is
20 dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 3

Dissolution rate of ethinylestradiol from tablets in vitro

The rate of dissolution of ethinylestradiol from tablets prepared as described in Example 1 was determined according to the USP Paddle Method as described in Example 2 for drospirenone. The results appear from Figs. 3 and 5 showing the dissolution rates from
30 tablet cores and film-coated tablets, respectively. In both cases, more than 70% of the active agent was dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 4

Bioavailability of drospirenone and ethinylestradiol from tablets containing 3 mg of drospirenone and 0.03 mg ethinylestradiol

5

42 healthy women between 18 and 35 years of age were included in an open-label crossover study after their informed consent had been obtained. The aim of the study was to investigate the relative bioavailability of drospirenone and ethinylestradiol from a tablet formulation containing 3 mg drospirenone and 0.03 mg ethinylestradiol with reference to
10 an oral suspension containing 6 mg of drospirenone and 0.06 mg ethinylestradiol per vial.

The bioavailability was determined using serum concentrations of each active agent as parameters. Compared to the oral suspension, the relative bioavailability of drospirenone and ethinylestradiol from the tablets is 107% and 117%, respectively. It was therefore
15 concluded that both drospirenone and ethinylestradiol are completely released from the tablets in vivo.

The absolute bioavailability of drospirenone was determined in two studies to be 76%±13% after oral administration of 2 mg drospirenone to 8 young healthy women and
20 85%±24% after oral administration of a microcrystalline suspension containing 3.13 mg drospirenone to 6 postmenopausal women.

The oral bioavailability of ethinylestradiol was determined in several studies, and mean values of from 36% to 59% were reported in the literature, indicating a first-pass effect.

25

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

30 An open-label, randomized trial with 52 female volunteers aged 20-35 years whose informed consent had been obtained included 1 pre-treatment cycle, 3 treatment cycles with two different tablet containing 2 mg and 3 mg drospirenone, respectively, but otherwise corresponding to the tablets prepared in Example 1, and a follow-up phase. A wash-out phase of 1 month preceded the treatment.

35

At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17 β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon.

Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactine, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum
5 glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly
10 reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the accompanying ultrasound examinations. Follicular ripening occurred in several cases with both trial preparations. Although three ovulations were diagnosed with the preparation containing 2 mg drospirenone (one of which was described as "equivocal" and the other
15 as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$) between the two trial preparations as regards the hormones LH, FSH, estradiol and progesterone, and the parameter "ovulation during the treatment cycles". In keeping with the hormones, cervical function was greatly limited and the "spinnbarkeit" and crystallisability of the cervical mucus was greatly reduced with both trial preparations.
20 Prolactin increased minimally and SHBG and CBG distinctly with both preparations. Triglycerides and HDL levels increased with both trial preparations, while LDL levels decreased. Total cholesterol was largely unchanged in both treatment groups. Oral glucose tolerance remained virtually unchanged or was slightly decreased. Testosterone, androstenedione and DHEA-S decreased minimally.

25 The subjective and objective tolerance was good with both treatments. This was also the case for cycle control with the exception of the first cycle with 2 mg drospirenone. Blood pressure, heart rate and body weight remained constant in the majority of cases or showed a slight tendency to decrease.

30 After three months' treatment, it was concluded:

The two trial preparations were equally good as regards the subjective and objective tolerance.

No negative metabolic effects were observed with either preparation. HDL was influenced positively in the sense of an increase.

The results confirmed the results of earlier studies that the 2 mg drospirenone preparation was in the threshold region of ovulation inhibition, whereas the 3 mg drospirenone
5 preparation had a demonstrable ovulation-inhibiting effect in all cases examined.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding U.S. application 09/386,274, are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

007220 2245950

CLAIMS

1. A pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount
5 corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.
- 10 2. A composition according to claim 1 wherein the drospirenone is in micronized form or sprayed from a solution onto particles of an inert carrier.
3. A composition according to claim 1 or 2, comprising drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about
15 3 mg.
4. A composition according to claim 1 wherein the ethinylestradiol is in micronized form or sprayed from a solution onto particles of an inert carrier.
- 20 5. A composition according to claim 1, comprising ethinylestradiol in an amount corresponding to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.
6. A composition according to claim 1, comprising an amount of drospirenone
25 corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg, in particular comprising an amount of drospirenone corresponding to a daily dosage of about 3.0 mg and ethinylestradiol in an amount corresponding to a daily dosage of 0.03 mg.
- 30 7. A composition according to claim 1 wherein the pharmaceutically acceptable carrier or excipient is selected so as to promote rapid dissolution of the first and second active agents.
8. A composition according to claim 1 wherein at least 70% of the first and second active
35 substance are released within 30 minutes of administration thereof.

9. A composition according to claim 8, wherein at least 80% of the first and second active agents are released within 20 minutes of administration thereof.

5 10. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

10

11. A preparation according to claim 10, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.

15

12. A preparation according to claim 10 or 11, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.

20 13. A preparation according to claim 10, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

14. A preparation according to claim 13, which additionally comprises a number of daily
25 dosage units comprising the combination of drospirenone and ethinylestradiol of 21, 22, 23 or 24, and a number of daily dosage units containing no active agent of 7, 6, 5 or 4.

15. A preparation according to claim 10, wherein the at least 21 daily dosage units
30 comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution onto particles of an inert carrier.

16. A preparation according to claim 10 wherein the at least 21 daily dosage units
comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular
about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg,
35 in particular from about 0.015 mg to about 0.03 mg.

17. A preparation according to claim 10, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

5

18. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2
10 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

19. A preparation according to claim 18, wherein the number of daily dosage units
15 comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.

20. A preparation according to claim 18 or 19, wherein the at least 21 daily dosage units
20 comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution onto particles of an inert carrier.

21. A preparation according to claim 18, wherein the at least 21 daily dosage units
comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular
about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg,
25 in particular from about 0.02 mg to about 0.03 mg.

22. A preparation according to claim 18, wherein the at least 21 daily dosage units
comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and
ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

30

23. A method of inhibiting ovulation in a mammal, in particular a human, comprising
administering, to said mammal, drospirenone in an amount in the range of from about 2
mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about
0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said
35 mammal.

24. A method according to claim 23, wherein the amount of drospirenone is in the range of from about 2.5 mg to about 3.5 mg, in particular about 3 mg of drospirenone per day.

5 25. A method according to claim 23, wherein the amount of ethinylestradiol is from about 0.015 mg to about 0.04 mg, in particular from about 0.015 to about 0.03 mg per day.

26. A method of preventing or treating androgen-induced disorders in a female mammal, in particular a female human, comprising administering, to said mammal, an amount of
10 drospirenone in the range of from about 2 mg to about 4 mg per day, together with an amount of ethinylestradiol of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to prevent or treat androgen-induced disorders in said mammal.

27. A method according to claim 26, wherein the androgen-induced disorder is acne.
15

28. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed
20 by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively administering no daily dosage units for 7 or less consecutive days.

29. A method according to claim 28, wherein the daily dosage units comprising the
25 combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein no daily dosage units or daily dosage units containing no active agent are administered for 7, 6, 5 or 4 consecutive days.

30. A method according to claim 28, wherein the daily dosage units comprising the
30 combination of drospirenone and ethinylestradiol are administered for 28 consecutive days.

31. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or
35 3, times 28 consecutive days, followed by administration of the daily dosage units

comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units containing no active agent, or alternatively no daily dosage units, for 7 consecutive days.

- 5 32. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit
10 containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

33. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone
15 are administered for 7, 6, 5 or 4 consecutive days.

34. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units
20 comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

35. A method of promoting rapid dissolution of drospirenone from a unit dosage form on
25 oral administration, the method comprising providing drospirenone in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone.

ABSTRACT

- A pharmaceutical composition comprises, as a first active agent, 6 β ,7 β ;13 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount
- 5 corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.
- 10 In a specific embodiment, the composition consists of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises the combination of drospirenone and ethinylestradiol. The composition may further comprise 7 or less daily dosage units containing no active agent or containing
- 15 ethinylestradiol alone.

00750 2245360

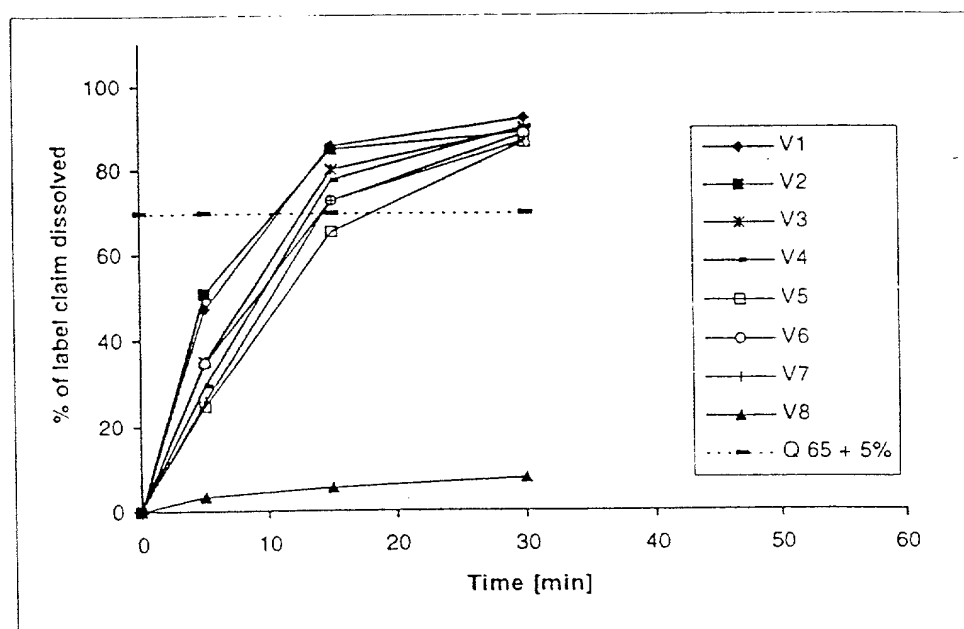


Fig. 1

2/5

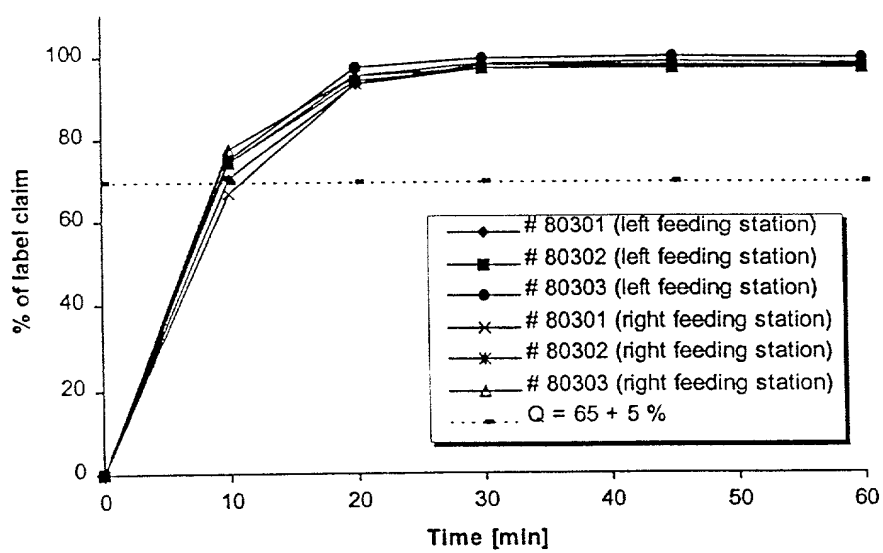


Fig. 2

3/5

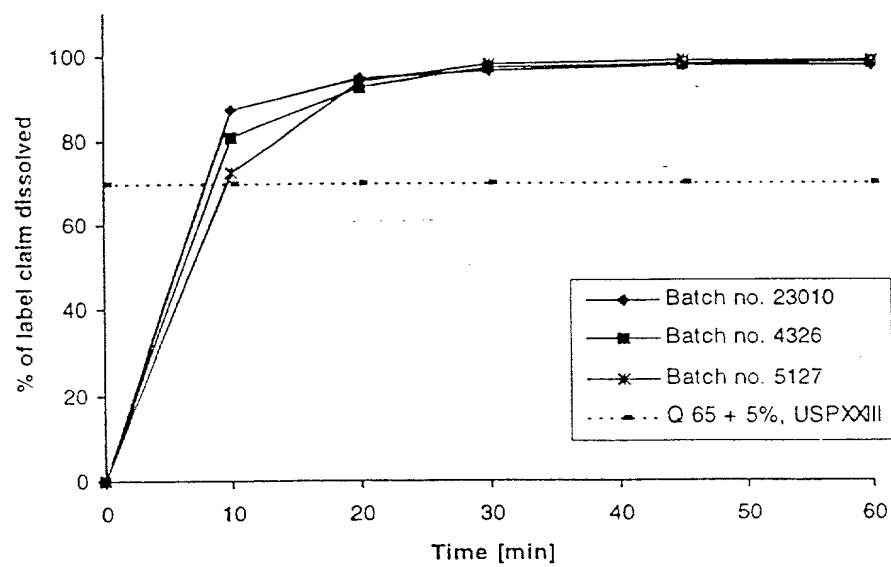


Fig. 3

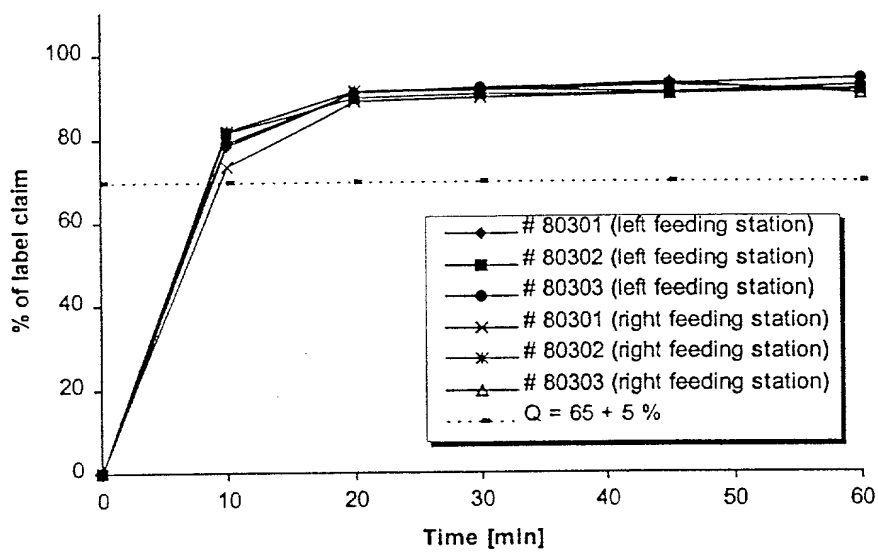


Fig. 4

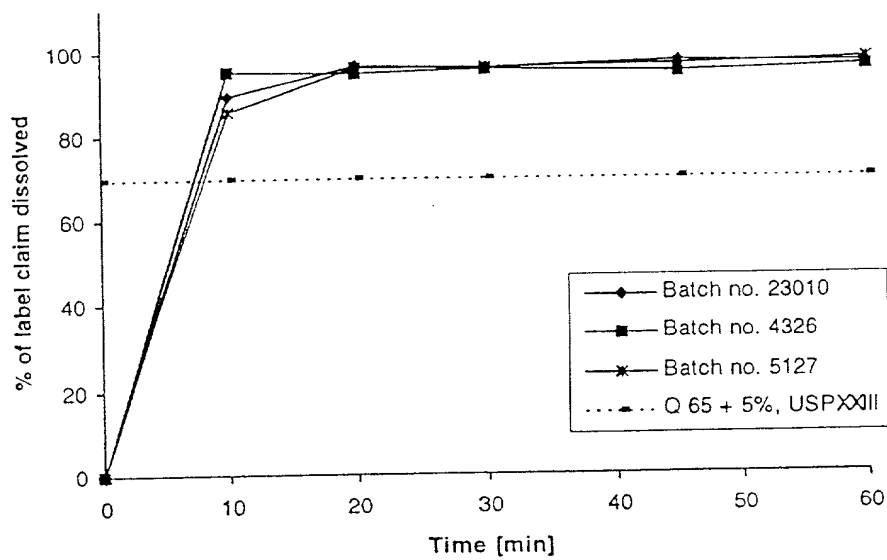


Fig. 5